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Student Medicine

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The Gannett Medical Clinic

The Gannett Medical Clinic

THESE columns carried in the April 1955 issue an announcement of a gift to Cornell University by the Gannett Newspaper Foundation. This gift, to honor Frank E. Gannett, was to provide a student medical clinic building on the Cornell campus.

In the intervening months we have watched with interest the construction of the Gannett Clinic, and we are now happy to announce its completion. Formal dedication will have taken place by the time this comes from the press.

This modern building, designed with what we believe is an exceptional blending of beauty and function, should serve as an outstanding tribute to an alumnus of Cornell who has maintained great interest in the University and has served as a trustee for thirty-one years. It seems especially fitting that such a tribute takes the form of a student medical clinic, for Frank Gannett is particularly interested in the welfare and health of students.

It is our belief that these fine physical facilities will stimulate and assist those who work in them to provide the very best of medical care and thus to justify the decision of the Gannett Newspaper Foundation to honor Mr. Gannett through such a gift to Cornell University.

Editorial Comment

SCIENCE AND THE "ART OF MEDICINE"

THE case report and its discussion by Drs. Schuldes and Wightman illustrate the point that despite the diagnostic and therapeutic developments of modern "scientific" medicine there still remains a critically important area where only the "art of medicine" as practiced by a skilled physician can provide the proper management of the patient.

A crucial point in the case history concerned the diagnosis of rheumatic fever. Science has so far failed to provide a specific test that will enable the physician to establish this diagnosis with certainty. The results of available tests and the signs were compatible with a diagnosis of acute recurrent rheumatic fever, and when on the seventh day of illness the conduction time as determined from the electrocardiograph was prolonged the diagnosis seemed definitely established. The subsequent reporting of a positive blood culture, which took fifteen days to grow out, cast doubt on the diagnosis of acute rheumatic fever. This information, which was so long delayed, was critical in management of the case, and lack of it resulted in a decision to institute treatment with adrenal steroids in the belief that the diagnosis actually was rheumatic carditis. Steroid therapy may have been deleterious in this situation, contributing to the difficulty in controlling the infection.

The cause of the prolonged conduction time is not certain. It is possible that it may represent evidence of rheumatic carditis, but the subsequent developments favor the view that it was the result of a focal lesion, probably embolic in origin, which involved the conduction fibers of the heart. In either case, the electrocardiograph did not indicate a definite diagnosis.

Later in the course of illness the roentgenogram of the chest

showed haziness at the base of the left lung. The reason for this increased density could not be specifically determined, the radiologist who interpreted the films suggesting at least three possible causes: (1) pleural thickening, (2) inflammatory process of the lung itself, or (3) compression of the lung tissue by the enlarged heart. A few days later the x-ray findings were characteristic of pericardial effusion. The x-ray examination thus failed to indicate the cause of increased density in the lung, and only after repeated examination was it possible to demonstrate that the cardiac enlargement was largely due to pericardial effusion. The etiology of this effusion could not, of course, be determined by x-ray examination. Radiography therefore had definite limitations in this case.

It is our purpose not to deprecate the value of radiography and laboratory procedures but to point out that the "art of medicine" is still a fundamental of which the successful physician must be master. He must be alert to avoid putting too much emphasis on laboratory procedures to the exclusion of careful history taking and physical examination; he must treat the patient—not the abnormal findings reported by the laboratory.

Treatment, too, must not be rule-of-thumb, must not merely follow the latest fad utilizing the newest miracle drug. As already mentioned, the use of steroids may have been deleterious in the case under discussion, although at the time treatment was begun the evidence of blood-stream infection had not been obtained. Even if the diagnosis of acute rheumatic fever had been sustained, adrenal steroids might have proved ineffective, for their value in this condition has not been fully agreed upon. It appears to be the case when they are used that the long-term outlook is not much altered, even though the acute symptoms may be greatly ameliorated. The undesirable and even dangerous side effects and complications arising from steroid therapy have been well publicized. Since the newer steroid compounds are not entirely free from such dangers, the physician must carefully weigh all factors before beginning their use.

College Environment as a Factor in Mental Health*

BENSON R. SNYDER, M.D., WELLESLEY COLLEGE

> "*No man is an island, entire of itself; every man is a piece of the continent, a part of the main.*"
>
> —DONNE

THE healthy adolescent moves toward separating himself from home. He develops increasingly final commitments in new and strange areas. For this to occur effectively his own image of himself must become distinct. He must find his own unique and meaningful identity. He must know himself. Such knowledge is not acquired easily, but only through a dynamic, continually shifting process. Erik Erikson expresses this task of adolescence as follows:

> This period of adolescence can be viewed as a *psychological moratorium* during which the individual through free role-experimentation may find a niche in some section of his society, a niche which is firmly defined and yet seems to be uniquely made for him. In finding it the young adult gains an assured sense of inner continuity and social sameness which will bridge what he *was* as a child and what he is *about to become*, and will reconcile his *conception of himself* and his community's recognition of him.[1]

There was a time when it was enough to define mental health as the absence of mental disease. Definition by exclusion is a

* Presented at the Annual Mental Health Forum of the New York State Society for Mental Health, Rochester, New York, October 22–23, 1956.

[1] E. Erikson, The Problem of Ego Identity, *J. Am. Psychoanalytic Assoc.*, *4*: 66–67, 1956.

reasonable starting point, but it does not carry our understanding far enough. A positive statement of mental health is a far more difficult and complicated assignment. It demands some precise notions about the "healthy" mind. It requires considerable sophistication of the intrinsic and external forces that lead to the dynamic equilibrium called health.

Our task is to consider one facet of this complex field, the college environment. This is permissible and will not lead us astray as long as we keep in mind the complexity and interrelationships. We cannot know the whole by knowing only one or several of the parts—especially since the whole is different from the sum of the parts.

The definition of mental health is difficult enough when applied to one individual. The difficulty is certainly compounded when one attempts a definition of mental health that applies to a group or to many groups from dissimilar backgrounds. Furthermore, many questions are raised by the title "College Environment as a Factor in Mental Health." Whose mental health? The students'? The teachers'? The deans'? There are other questions. Having defined mental health, how can one be certain a given individual possesses it?

It is not possible to characterize the atmosphere of a college in a few sentences without writing what will seem like a caricature. Nor will it be possible to answer all the questions that have been raised. The generalizations and observations that follow are not intended as blueprints or pronouncements but rather as leads to a useful approach by which the interaction of college and student can be understood.

Much of the material that forms the basis for discussion comes from the First International Conference on Student Mental Health, held in Princeton this past September. Dr. Dana Farnsworth was the very able chairman of this meeting. First, we will review several brief observations on the effect of three foreign college environments on their students. Then some comparisons can be made with colleges in the United States. Finally, certain trends will be seen to be common to these apparently very different situations.

The following questions raised by Erik Erikson are particularly relevant to the consideration of these colleges:

1. What is the relationship of the college environment to the larger culture in which it functions and of which it is a part?

2. What is the relationship of the college environment to the specific earlier environment of its students? What degree of continuity does the student experience in his meaningful relationships, first in the family and later in the college?

3. What are the specific ways in which the college emotionally supports its students? What factors in the college environment create anxiety in the student?

Dr. Daniel Douady, Director of School and University Hygiene in the Ministry of National Education in Paris, described at Princeton the conditions of the French student in some detail. There are striking differences between the student's situation as we know it and as it exists in France. Many French students are desperately poor and may have to travel ten miles or more each day from their lodgings in a cheap boarding house to the university. Some students have no lodgings and sleep in the hallways. Many do not have sufficient money for food or proper diet. There is, further, a brutal transition for the student when he leaves the ordered and highly structured atmosphere of the lyceé and moves into the freedom of the university. Here he is completely on his own. There are often 500 students in his lectures. His classroom neighbors are never the same. He may work independently for two years or more before taking his first examination, with almost no contact with faculty and little with students. These are some of the factors that encourage physical and psychological isolation. There may be nothing for the student to hold on to, and the university's attitude is often that the student can sink or swim. Roughly 50 per cent fail.

Dr. Douady described some of the more common pathological reactions among French students: (1) The need to play a role, to be all the time very complex, cynical, or blasé. The grave risk here is that the student will get caught in his own game. (2) *L'hyperintellectualization.* To translate this as intellectualization does not do it justice. He observed that intellectual activity

among this group of students becomes overevaluated at the expense of all action. A disequilibrium follows in which there is disregard of the real world and of daily issues and the student seeks refuge in rigid intellectual systems and abstract ideas. At the same time, the student will regard even the overevaluated intellectual process with contempt. This, then, will lead to depression, to poor reality testing, and to a general impoverishment of affect. It is a tragic and all-too-frequent occurrence. (3) Emotional problems. These manifest themselves in many ways: in the need for dependence on parents or parent surrogates, in open revolt, or in revolt camouflaged under many forms of submission.

It is always difficult to separate two or three factors from a vastly complicated, almost kaleidoscopic, picture and say, "These are the relevant considerations"; but certainly one such important consideration would have to be the impact of the war and occupation in France on the way students approach new experiences. Students resent any *imposed* change and will fight it. They take the lead themselves in effecting change. This may be part of a general distrust of the adult world to be expected in young people who have grown up in an occupied country. They have an intense need for security and now begin to band together to improve first their economic lot and second their living conditions. And their action appears to be a partial attempt to reestablish a social structure similar to the dependent and rather clearly defined relationship that they experienced in their families during childhood.

The motivations of these psychological traits are innumerable, peculiar to each individual. However, certain actual conditions of the student's life in the university permit a reactivation of old conflicts. Thus, economic dependence and deprivation favor an emotional dependence. The need to play a role appears to be related to the vacuum into which the student moves when he leaves the lyceé and comes to the university. The university's almost total reliance on a few examinations, where the student is expected to "perform brilliantly" may well encourage *l'hyperintellectualization*, as a kind of intellectual game.

Dr. Brian Murphy of the Student Health Service of the Uni-

versity of Malaya in Singapore has made a careful and perceptive study of the cultural factors in the mental health of Malayan students. Many of his observations and findings are particularly germane.

The University of Malaya is patterned after British educational institutions. In England, however, a university degree is in no way essential for economic advancement, while in Singapore it is gradually becoming a necessity. It is almost the only way in which an individual can move from one social level to another or improve his economic position. Admission to the University is highly selective, there being 1,000 students in a population of 6,500,000. This ratio leads to fierce competition for admission. Since almost 90 per cent of the students are on some form of scholarship, the main hurdle that must be overcome is the entrance examination. Ironically, the educational system may be creating a new elite; certainly the students are a favored group.

Dr. Murphy thoughtfully describes some aspects of the culture of each of the three ethnic groups. He follows this with a careful analysis of the emotional disturbances seen in the students from these three groups. Because of the limitation of space only those conclusions which are relevant to our discussion are reported here.

In the final section of his paper, Dr. Murphy describes several instances in which cultural considerations form the basis of preventive mental health measures in the University; for example, many attempts were made by the University to provide father substitutes in the form of advisers or counselors. These attempts failed, since they were designed after the British model of father-son relationship and had little relevance for the student in Singapore. When the junior staff of the University was used in something like an older brother position, this also failed. The students did not understand the role assigned to the warden, or counselor, as he was called. The brother, in Chinese and Indian cultures, is almost uniformly an unsympathetic figure and rarely an easy companion. Dr. Murphy notes in contrast that the appointment of young wardens in a girls' hostel was most successful, and he relates this success to the sympathetic and trusted role of the older sister in all three cultures.

Dr. Murphy's concluding remarks deserve full quotation:

> Singapore's degree of cultural mixture, and the research which this permits, may appear unique; but it is really only an extreme example of something which we all have experienced. In all universities, doctors and lecturers come to recognize that there are group differences between the students from one part of the country and from another, or between one occupational class background and another.

The academic situation in Holland was described at the Princeton conference by Dr. Aride Querido. The status of the professor in the Dutch university approaches that of an autocrat. With tenure and the rank of full professor he achieves absolute authority over the academic lives of his students. It is usual for the professor to take the attitude that he is there to give the lecture and anything beyond that is the student's responsibility. There is a minimum of interest and personal relationship, and the professor remains distant and reserved. At the end of a certain period of time the student is given an examination which is the basis for his mark. There are occasional abuses. The professor may take a dislike to a particular student and fail him on a whim.

The student body appears to divide itself into two groups: those who belong to university social societies and those who do not. Roughly 40 per cent join one of these societies, which then serves as a focus for their life at the university. There are relatively few academic failures or psychiatric casualties in this group. The remaining 60 per cent are known as "nihilists." It is from this group that the students with academic or emotional difficulties come. Many of the "nihilists" seem to give up before they begin and react to the authoritarian position of the professor by withdrawal, by an essentially depressive maneuver, while those who band together in societies take some strength from this and are less overwhelmed by or less exclusively dependent upon their relationship to their professor. Personality factors are, of course, present before the student's university experience and will play a major role in determining which way he will go. It does look, however, as though the university has institutionalized a type of relationship between teacher and student that will reinforce an already neurotic pattern and further reduce the possibility of a reintegration of the ego on a more mature level.

One can understand these separate observations by referring to the type and quality of collaboration of teacher and student. The point to stress is that such collaboration is finally achieved after a period of negotiation. This negotiation is influenced by what the student brings with him to the university, as well as by what he finds at the university. There are elements of what we would call transference in the student's relationship with his teacher. It must be emphasized, however, that the teacher and, beyond that, the institution may have a *direct* impact on ego development. Certain defensive patterns in the student are acceptable and encouraged; others may be forbidden by either teacher or university. Thus the external cultural definition of the role of student vis-a-vis the teacher is overdetermined and becomes a part of the internal life of the student.

The relationship that develops between teacher and student will be further significantly influenced by the relationship that exists between the institution and the student peer culture and between the teacher and the institution. The teacher who must hold his own inner world rigidly together may be unable to communicate freely, for example, with the not uncommon heretical sophomore, the "hyperintellectual" in France, or the "nihilist" in Holland. It is also evident that the teacher's attitude toward his students is determined not only by inner tensions and needs but also by such prosaic matters as tenure, salary, academic freedom, and academic prestige. These last factors may not be a conscious concern of the teacher but may find expression in some vague doubt about his role, his competency, his goal as educator. There are situations where this doubt subtly interferes with the teacher's effectiveness and his ability to communicate his subject to the students.

The student, on his part, will tend to relate to his teachers on the basis of his earlier experience with his parents. The counseling programs at the University of Malaya failed to take into account sufficiently the fact that the parental relationship will give individual structure to the student-teacher relationship. This structure in itself will not necessarily determine how much learning or growth occurs in the student. Much of what is known in psychoanalysis about this process of education has come from intensive

study of failures. However, extensive experience in an educational institution is hardly necessary to demonstrate that the normal educational successes derive, in part, from the atmosphere for learning in the college. This atmosphere is the expression of many factors in the student's life—his teachers, certainly, but also his experience in his dormitory, in college government, and in dating. The admission policy of the particular college and its academic or social prestige may also be crucial here.

Another factor which deserves special emphasis is the university's reaction to group and individual differences in its students.

Some colleges even in America demand conformity and tolerate no deviation from the group practices. This conformity is expected of faculty and students alike. One would expect the admission policy of such an institution to be selective and restrictive. There was a time when such a college would proudly and consciously consider its task the development of an intellectual or, more properly, a social elite. The shift in values in our culture has led to greater discretion in the statement of the aim, even though the aim itself may not have been abandoned. In contrast to colleges for the elite, one can find educational institutions that do not choose to recognize the existence of group differences. They demand tolerance rather than conformity and admit students from all ethnic and economic groups. In an extreme form, there is some risk that this approach also puts a heavy burden of conformity on its students. It can be as rigid and inflexible as the first type of college mentioned. Many colleges and universities encourage "cultural mixing" somewhat similar to the situation in Malaya. Here there is a recognition of the differences between groups, and active interchange is encouraged between groups. A final variation on this theme would be the college that considers the individual to the exclusion of the group. It is suggested that the specific atmosphere for learning in a college is closely related to just such factors as these.

We return now to the three specific questions that were raised earlier, the three which you were asked to keep in mind. We could take any one of the American universities, or any foreign college, and work out the relationship that exists between the college and its culture. The mental health implications of too

great a discrepancy between college and culture will be apparent from the following brief clinical example:

An eighteen-year-old boy from a ranch in Utah came to an ivy league college and experienced a profound degree of shock and estrangement. As he put it, "the bottom fell out." He was a very able boy and his ensuing academic failure surprised his teachers. In addition to the specific psychodynamic factors that accounted for his turmoil, we must add the overwhelming impact of the change which confronted him—a new and unfamiliar set of moral values, a change in attitudes toward money. He heard family and sex talked about with disturbing frankness.

The college must expect and anticipate such reactions. There is always the risk that, like the French student, the boy from Utah may simply learn to play a role, play a part in college. Buying an ivy league suit will not help him with the strangeness and isolation he feels any more than "hyperintellectualization" solved the same dilemma for his French counterpart.

The second question that was raised involved the relationship of the college environment to the student's earlier environment. When there is too little continuity between family and university, as seemed to be the case among the Malayans in the University of Singapore, certain students may well feel lost. Conversely, the college may represent a new edition of old family relationships to a striking degree. For example, there is evidence that some girls who attend women's colleges, with their predominantly female faculty, may reactivate their old conflicts with mother and expend much energy in the ensuing neurotic struggle. From what we know of adolescents, it is clear that the student needs new and positive identifications with real people who are strongly committed in their own right. The emphasis is on the need for a new identification, not simply a substitute for an old one. But in order for identification to occur it must have some relevance to the student's earlier experience.

The nihilist is not limited to the Dutch university. "Apathy Clubs" have recently been formed on several campuses in this country. The problem is not always spelled out for us so plainly. It is usually very much overdetermined, as is illustrated in the following example:

STUDENT MEDICINE

A talented sophomore in an eastern university was failing in chemistry. His father, an alumnus, had done well in the same course but had later stopped short of his Master's degree. His considerable success in business did not altogether compensate for the failure he felt in leaving graduate school. The father was certain his son was born to be a chemist. There was no evidence that this notion of the father's had ever been congenial to the son, who had expressed some of his resentment about this point by a relentless and ingenious teasing of his father. A portion of the normal rebellion of adolescence also came out here.

It is clear from what has been said that the son was already very sensitive about the matter of his doing work in science before coming to college. The college added to the problem in the following way. The particular course was required; he could not substitute another science, for example. The difficulty was further compounded by the unhappy coincidence that the teacher used almost the same words as the parent had before to urge this student to do well. The student responded with teasing, and, understandably, the teacher responded to this with anger. An impasse developed. It may be said that the college's responsibility for the impasse lies in its failure to provide a sufficiently flexible environment. It did not provide an opportunity for the student to develop an intellectual commitment by means of a new identification with the teacher. Instead of seeing chemistry in a new way, he immediately recognized the old familiar pattern. The environment here had reinforced an earlier neurotic adaptation. The impasse was eventually resolved by the student's giving up any active fight and becoming apathetic; in a way familiar to the Dutch student referred to earlier, he withdrew.

I must state a word of caution before suggesting a frame of reference designed to help us understand the ways in which a college can support its students or the ways in which it may create pathogenic anxieties in its students. There is a tendency, especially in America, to translate a theory or hypothesis into a plan of action before all the implications of the theory are fully understood. In other words, I do not suggest that we make a check list of those areas where the college seems to support the student, reinforce those areas, and do away with the areas that

create anxiety. It is obviously not that simple. Indeed, it may remind you of Anna Freud's comments on the need for tension:

> In periods of calm in the instinctual life, when there is no danger, the individual can permit himself a certain degree of stupidity. In this respect, instinctual anxiety has the familiar effect of objective anxiety. Objective danger and deprivations spur men on to intellectual feats and ingenious attempts to solve their difficulties, while objective security and superfluity tend to make them comfortably stupid. Focussing of the intellect on instinctual processes is analogous to the alertness which the human ego has found to be necessary in face of objective changes which surround it.[2]

In order to understand the influence which the college environment has on the mental health of students, we must have some reference point, some model, which would apply equally to all the variations that we have discussed previously. If we return to Erikson's concept of the task of adolescence we can see that we are talking about a state of productive tension in the student. When the tension becomes too intense, it may well become destructive. If it diminishes or is absent, we may well have apathy. One can see that a dynamic equilibrium exists between the student's environment and the student himself. The college environment should assist in the liberation of the student so that he is able to think in new dimensions and form new relationships.

The following brief clinical example will highlight and illustrate these points: A junior had gone through two and a half years of college doing average work with little effort and less commitment. She was an exceptionally gifted young woman, but in her home and in her group at college she felt it was not acceptable to be "too bright." "Being excited" had no place in her picture of the suburban matron. In some ways she saw herself like the French students—as blasé. During a course in art history she was assigned a paper on a particular sixteenth-century painting, a Pietà. She became deeply curious about its authenticity, studied the glazes and pigments in use at the time, its composition and form, with great excitement, and then decided the painting came from an earlier period and was done by another artist.

[2] A. Freud, *The Ego and the Mechanisms of Defense* (New York: International Universities Press, Inc., 1946), p. 179.

It is not so important whether she was correct. Her teacher had been able to stimulate the student's curiosity with an exciting learning experience. She gave the student permission to question in her own right. Her curiosity, previously inhibited, had been freed in the service of intellect. This experience, the painting itself, and questions she asked about it, all had a high degree of significance for this student in terms of her earlier curiosity about her family. The moderate inhibition of this curiosity had taken a heavy academic toll. It was in part the relationship with a sensitive adult strongly committed to her field that made it possible for her to release enough of the inhibition to answer the question, "What do you really think?"

The adolescent needs the opportunity to experiment with various roles; he needs an adult who understands him but will not force that understanding. He needs to develop new and constructive ways to use his energy.

Neurotic or psychotic crises use up this energy in the defensive struggle, leaving the individual with a feeling of isolation and emptiness, with a diffuse and vague self-image. In a negative sense, the environment can have a similar, though probably less drastic, effect by limiting the role of experimentation, by putting a too-rigid fence around the energy, by offering little or no opportunity for new and healthy identifications. However, we have seen that the college must provide some limits, some kind of fence. It must help the student to control and harness his instinctual energy.

I have suggested that we are discussing a dynamic equilibrium —an equilibrium maintained by many factors in the college as well as by what the student brings with him to college. The college can have some effect on its students, on their goals and their aspirations. It can improve the effectiveness of this equilibrium or impair it. This is not to say that the college, by simple environmental manipulation, can effect the total removal of neurotic patterns in students. It cannot. The effect of the college environment can be such as to avoid reinforcing neurotic patterns and to facilitate a constructive liberation of the individual's potential so that he becomes less prone to self-deception and self-defeat.

Bacterial Endocarditis with Pericardial Effusion, Report of a Case

RUDOLF E. SCHULDES, M.D., AND
HENRY B. WIGHTMAN, M.D., CORNELL UNIVERSITY

THE problems which arise in the diagnosis and treatment of such a complex and incompletely understood disease as rheumatic fever multiply if one is confronted with the appearance of a superimposed bacterial endocarditis in a known rheumatic patient. The following case report illustrates the difficulties in making a correct initial diagnosis and in deciding the form of therapy to be used once the diagnosis is made. Complicating endocarditis, myocarditis, and pericarditis further confuse the picture. Forms of therapy are at times in conflict, so that preference has to be given to the more serious complication.

CASE REPORT

An eighteen-year-old white male was admitted to the Cornell University Infirmary on January 13, 1955. The family history was unrelated; his personal history disclosed that he had had a tonsillectomy at the age of two and an appendectomy when he was twelve. At the time of the appendectomy he was ill for six months with a febrile disease which was finally diagnosed as rheumatic fever and which left him with a compensated aortic insufficiency. During subsequent winters, including the present one, he had received prophylactic penicillin orally with no recurrence of rheumatic fever. Electrocardiograms in 1950, 1952,

and 1954 were within normal range. Physical examination on entrance to Cornell University in September 1954 disclosed basal diastolic and apical systolic murmurs.

On admission, the patient complained of general malaise, slight headache, sore throat, nasal congestion, chilliness, and fever. He stated that on the previous day, January 12, he had received minor dental treatment for a small canker sore on the gum of the left upper third molar.

Admission examination revealed a well developed, acutely ill white male whose rectal temperature, pulse rate, and respiratory rate were 101.2°, 94 per minute, and 20 per minute respectively. The reclining blood pressure was 122/40. Within two hours the temperature rose to 103.5° (oral), when the patient appeared somewhat dyspneic. There was redness of the throat and mild lymphadenopathy of the cervical glands. The thorax and lungs were normal. The heart was enlarged to the left and a harsh diastolic murmur was heard over the aortic area. Although there was moderate tenderness over the hepatic area, the liver was not palpable and no masses were felt in the abdomen. All superficial and deep reflexes were present and equal. An initial chest x-ray (Fig. 1) showed the lung fields clear, but the transverse diameter of the heart was 25 per cent above average. Laboratory data on admission revealed a white blood count of 33,500 with a differential of 22 stab cells, 68 segmented cells, 31 lymphocytes and 1 monocyte. The urine was cloudy amber in appearance, had a specific gravity of 1.025, contained 50 mg. per cent of albumin, no sugar, 10–15 white blood cells, a few red blood cells, and a few granular casts.

On the second day the oral temperature remained 103.8°, pulse rate was 96 per minute, and, in addition to the findings on admission, over the chest there was a fine sudemic rash, which disappeared within twenty-four hours. The tenderness in the right upper abdomen persisted; neither liver nor spleen was palpable. On the third day the white blood count was 34,000. Therapy during the first three days consisted of penicillin, 600,000 units every twelve hours. On the third day dihydrostreptomycin, 1 gm. b.i.d., and achromycin, 0.25 gm. every six hours, were added. From the fifth through the seventh day the temperature

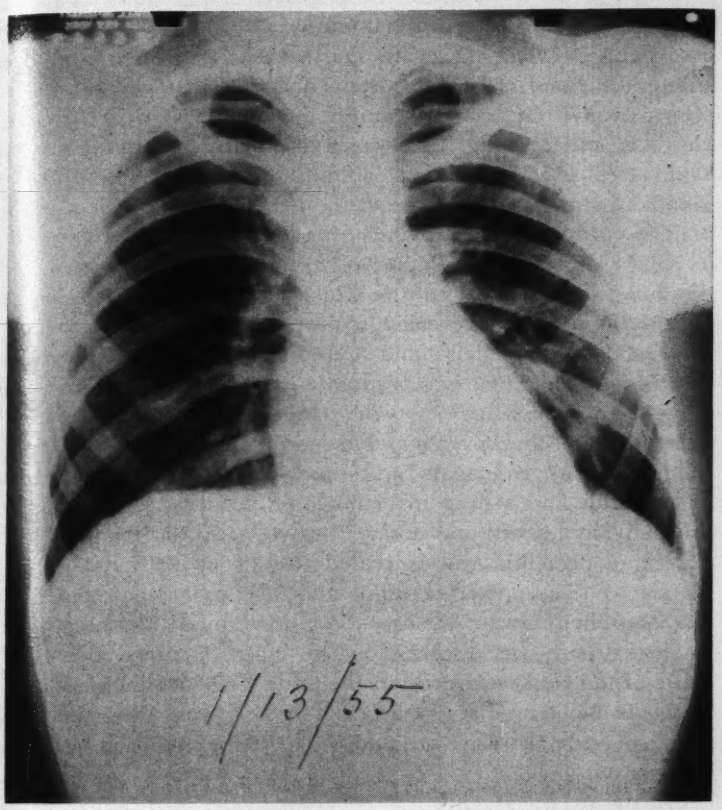

Figure 1. Posteroanterior roentgenogram of the chest (at 2 meter) on admission. Heart shows considerable left ventricular enlargement, maximal transverse diameter of the cardiac shadow 15.7 cm., 25 per cent above the expected normal. Lung fields show no evident pathology.

was somewhat lower and the white blood count dropped to 22,000. The hemoglobin level declined from 12.5 gm. to 11 gm. An electrocardiogram on the seventh hospital day revealed an increased PR interval of 0.28 sec. but no other abnormality. The heart appeared more enlarged to the left than on admission; the lungs were found clear. The presumptive diagnosis at this time was acute rheumatic fever with active carditis.

On the ninth day hydrocortisone was begun, the initial daily dose being 300 mg. (Fig. 2). During the next three days the temperature and pulse rate dropped and the patient appeared improved. Within five days the PR interval reverted to 0.16 sec. However, on the fifth day of cortisone therapy the temperature again rose to 103°, and a diminution of breath and voice sounds was noted at the base of the left lung. The patient complained of fatigue and of pains in the left flank. On the sixteenth day an antistreptolysin 0 titer of 8,530 units was reported. At the same time, a blood culture which had been obtained on the second hospital day revealed a growth of *Streptococcus viridans.* Massive doses of penicillin and streptomycin were started and the dose of hydrocortisone was gradually reduced.

During the next three days the temperature fell with considerable subjective improvement. However, after seventy-two hours the temperature rose again, and a renewed elevation of the white blood count and a drop in hemoglobin occurred. At this point the daily hydrocortisone dosage was reduced to 10 mg.; daily dosage of penicillin was increased to 12,000,000 units; Achromycin, to 12 gm., and sodium salicylate, to 5.2 gm. per day. The diastolic murmur was now more pronounced, but no change in cardiac size was discernible. The lungs remained clear. Because of the continued drop in the patient's hemoglobin, 500 cc. of whole blood was given. During the following days the temperature remained elevated, and the patient's condition began to deteriorate.

On the twenty-seventh day occasional rales were noted at the left lung base. An AP chest x-ray taken on the thirty-first hospital day revealed haziness of the left lung base. The differential diagnostic possibilities from the roentgenogram were pleural involvement, inflammatory process of the lung itself, or compression of the lung from an enlarged heart. During the next five days the temperature remained considerably elevated and the pulse rate was more rapid. There was an area of dullness at the left lung base over which bronchial breath sounds and fine rales were heard. The apical impulse of the heart was localized 2 cm. lateral to the left nipple in the fifth intercostal space, where a loud systolic murmur could be heard. There was no cyanosis. Despite good

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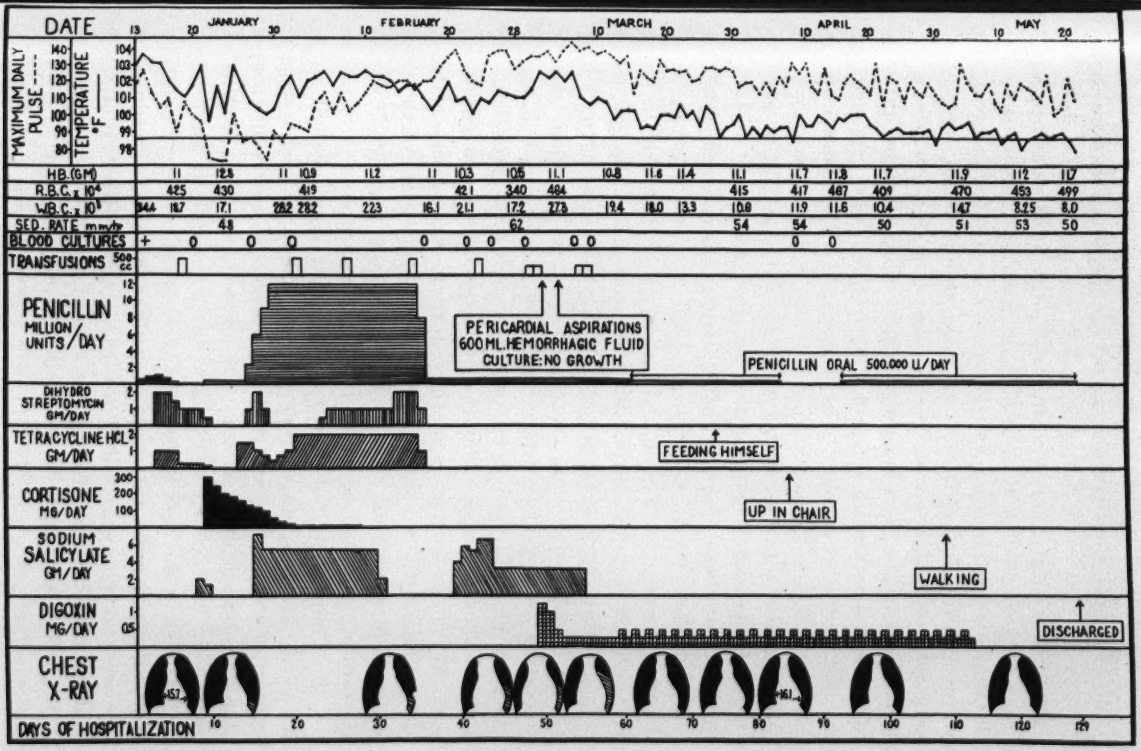

Figure 2. Graphic illustration of clinical and laboratory findings and of therapeutic measures used.

appetite, weight loss was evident. Meanwhile antibiotics had been continued.

On the thirty-sixth day all medication was discontinued with the exception of 600,000 units of penicillin daily. Following this, the temperature showed lowered trends for several days, although the pulse rate climbed to 120–130 per minute. Some reduction of the white blood count occurred; the hemoglobin level was kept at approximately 12 gm. by giving 500 cc. of whole blood weekly.

On the thirty-ninth hospital day, for the first time a to-and-fro murmur over the cardiac apex was heard. The next day the electrocardiogram showed slight elevation of the RT segment in leads II, AVF, V2, V4, and V6, suggesting the possibility of rheumatic pericarditis. The condition of the patient remained unchanged for several days, with the temperature remaining at a somewhat lower level; the heart rate, however, continued high at 120–130 per minute. The apical impulse shifted beyond the anterior axillary line, the pericardial rub continued to be loudest at the apex, and the diastolic aortic murmur was unchanged. There was no liver enlargement, no evident edema, no other sign of impending heart failure. Chest x-rays on the forty-fourth hospital day disclosed an enlargement of the superior diameter of the heart in the supine position in comparison with the semierect position. Pericardial fluid seemed to account best for this change.

The patient showed signs of increasing dyspnea and orthopnea with a respiratory rate of 36 to 40 per minute, pulse rate of 130 per minute, temperature elevation of 101°, and blood pressure of 130/40. The pericardial rub over the apex continued distinct; the liver enlarged; impending cardiac failure seemed evident. Because of the continued drop in the hemoglobin level, the patient was again transfused with whole blood, this time in divided amounts of 250 cc. per day. Signs of cardiac failure were more evident during the next three days as demonstrated by increasing dyspnea, rapid pulse rate, and oliguria. On the forty-ninth day digoxin and mercurial diuretics (Thiomerin) were begun. A chest x-ray on this day revealed marked increase in cardiac size, particularly to the right (Fig. 3). It was evident that pericardial fluid was increasing rapidly. On pericardial tap about 350 ml. of dark hemorrhagic fluid was obtained which resembled old blood.

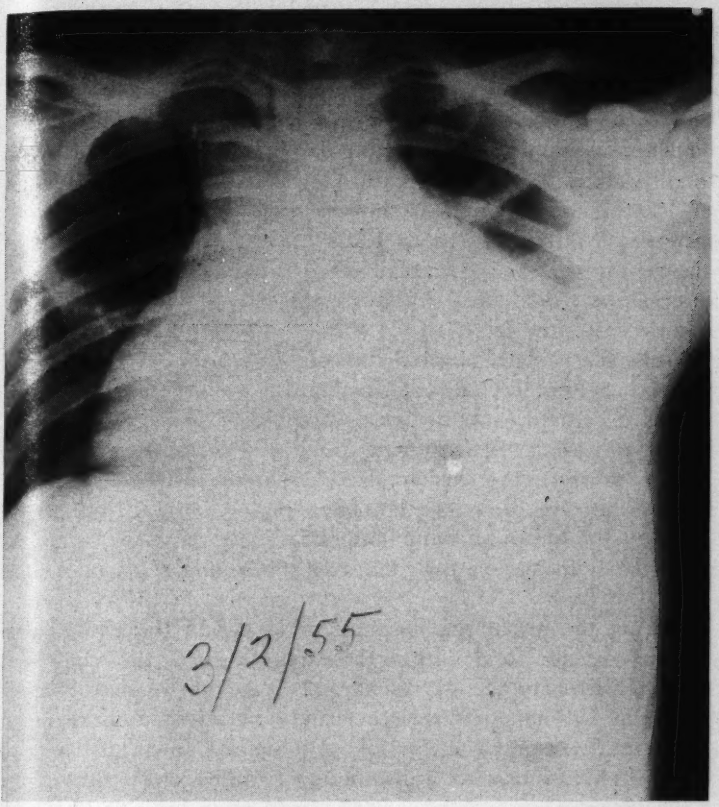

Figure 3. Anteroposterior roentgenogram of chest (bedside unit) on March 2, 1955, showing marked increase in cardiac size, particularly to the right, due to pericardial effusion.

The patient withstood the procedure well; respirations appeared less labored following aspiration. A chest film the next day showed about 1.5 cm. decrease in the size of the heart shadow at the base and some reduction of the right-sided enlargement. An increase in the friction rub was noted. The pericardial tap was repeated two days later and 250 ml. of dark, bloody fluid was removed. Cultures of both specimens were reported sterile. No organisms were seen in the smear. Digitalis therapy was continued.

During the three days after the last pericardial tap the patient's condition remained unchanged. Auscultation of the left lung revealed bronchial breath sounds and no rales. The chest x-ray showed no definite change in heart size but did reveal left lung field density, which was thought to be of pleural origin. From the fifty-sixth day on, temperature levels tended to remain lower, 99–100.6°, and the patient showed signs of improvement. The urinary output increased to 1,200 cc. in twenty-four hours. A chest x-ray three days later reflected this improvement; the left upper lung field looked relatively clear, and the heart shadow had decreased in size.

From the sixtieth hospital day on, improvement was steady; temperature became normal; anemia was less pronounced; leucocytosis decreased, appetite was satisfactory; urinary output returned to normal. Although the pulse rate remained elevated to 120 per minute, the cardiac size decreased, and by the eighty-fourth day the transverse diameter was 16.1 cm. compared to 15.7 cm. on the admission film. The enlargement was located particularly in the left auricular area. Both lung fields were clear (Fig. 4).

During the remaining hospitalization period the patient was able to increase his activity to the extent of sitting in a chair and walking with help. He was discharged on the one hundred twenty-ninth day for further convalescence at home. The patient reported that after five months he was able to go up and down stairs several times each day and to walk about two miles daily. The heart x-ray measurements showed further reduction in size. The sedimentation rate, hemoglobin, and white blood count were within normal limits, and a blood culture was negative. An electrocardiogram showed no abnormality. Since discharge from the hospital the patient has gained twenty-four pounds.

COMMENT

The two items of interest in the history are first, appendicitis at the age of twelve, which was later found to be rheumatic fever with abdominal symptoms, and, secondly, treatment of a gum infection the day before the present illness developed. This latter item is suggestive and occurred in spite of a daily prophylactic

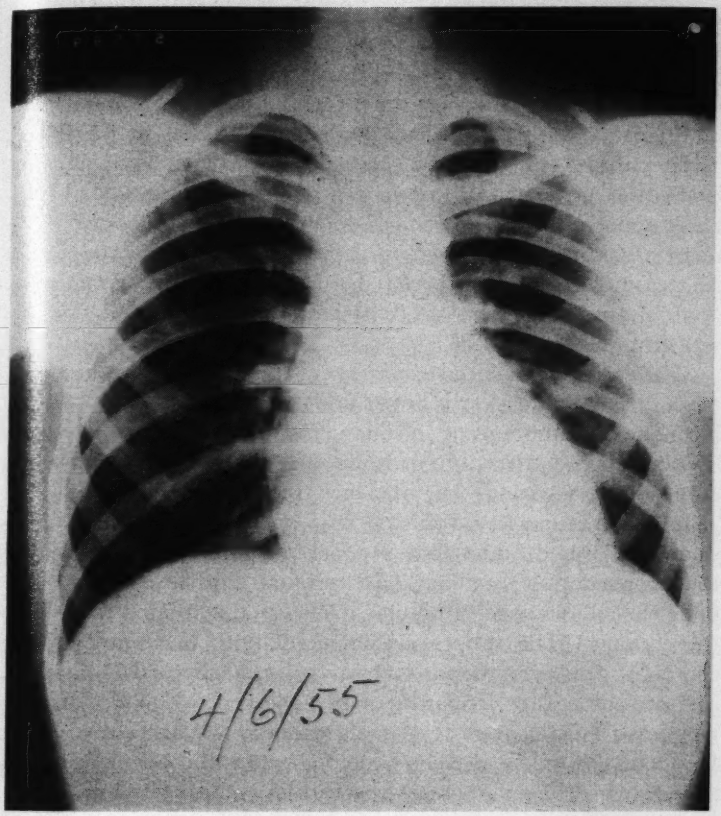

Figure 4. Posteroanterior roentgenogram of chest (at 2 meter) on April 6, 1955. Maximal transverse diameter of cardiac shadow 16.1 cm. Predicted transverse diameter, 12.5 cm. Both lung fields clear.

ingestion of 100,000 units of oral penicillin. Dental treatments, especially extractions, are known to be a potential danger to a previously damaged heart valve.

At the onset of the illness the reason for the patient's marked febrile state was not evident. Repeated observations including physical, radiological, and laboratory examinations did not reveal an infectious focus; thus, rheumatic fever recurrence was

suspected. The prolongation of the PR interval in the electrocardiogram on the seventh hospital day added evidence to the initial working diagnosis of this disease. Thus, it was decided to initiate treatment with cortisone. On the fifteenth hospital day, however, a positive growth of *Streptococcus viridans* in the initial blood culture was reported, necessitating a revision in clinical evaluation. At least, a combination of rheumatic fever and bacterial endocarditis had to be considered. In view of this development endocarditis appeared to deserve more consideration, and its treatment was given preference in therapy. Therefore, large doses of antibiotics were administered, and the cortisone therapy was gradually reduced.

At the present time the exact role of the corticoids in the treatment of rheumatic fever is better understood than the use of these hormones in intercurrent infectious diseases. In Hench's historic report [1] on the effects of cortisone on rheumatic fever the difficulties of evaluating the efficiency of ACTH, cortisone, and aspirin on rheumatic carditis became evident. The United Kingdom and United States Joint Report on Rheumatic Fever shows the proportion of patients with residual cardiac damage after one-year-follow-up to be similar in the groups treated with these three drugs.[2] The suppressive effect of both hormones on the rheumatic manifestations, such as fever, tachycardia, elevated sedimentation rate, impairment of atrio-ventricular conduction time, and anemia were repeatedly confirmed,[3] together with the fact that rheumatic activity recurred when the hormones were withdrawn before the disease reached its natural termination. In our patient a transient antipyresis, return of atrio-ventricular conduction time to normal, and slight subjective improvement took place after cortisone therapy was initiated. Except for the electrocardiographic change of the PR time to normal, the other improvements lasted only three days. After proof of streptococcemia was obtained, it is speculative whether or not the immediate discontinuation of the hormone therapy would have been deleterious to the patient.

The fact that infections become more serious and occur more frequently during ACTH or cortisone treatment is, up to the present time, more clinical experience than established laboratory

evidence. The mechanisms by which ACTH and cortisone influence infections were recently summarized by M. M. Montgomery *et al.*[4] The most unfavorable effect of cortisone in an infectious disease is probably the inhibition of inflammation. Even though bacterial invasion may be promoted, it seems that a bacteremia is not directly affected. Information concerning the influence of cortical adrenal hormones on bacterial endocarditis is based largely on animal experiments.[5] The incidence of experimental streptococcic endocarditis in rats that are not susceptible to bacterial hypersensitivity and in rabbits that are susceptible is not significantly different. Gross and microscopic characteristics of the endocarditis and the concentration of circulating antibodies are not different in these animals if large daily doses of cortisone are given. The dosage used clinically neither increases nor decreases the antibody production.[6]

For a period of eighteen days our patient received 12,000,000 units of penicillin daily, along with streptomycin and achromycin. During this time fever and leukocytosis remained unchanged, and the patient showed no evidence of improvement. Undoubtedly a relative bacterial resistance had taken place. The problem of antibiotic resistance seems to be much more serious in chronic infections. There is great danger that a resistant bacterial strain may be produced and cause increased damage resulting in the patient's condition becoming worse during the course of antibiotic therapy.[7] Most forms of enterococci and some gram-negative rods show a resistance similar to that of *Streptococcus viridans* strains under large doses of antibiotics.[8] Streptomycin and some other antibiotics are ineffective even in high concentrations against a rare colony in bacterial cultures if the initial innoculation of that strain is large enough. Consequently, a conversion to a predominance of resistant forms occurs. Erythromycin was shown to have a similar tendency with *Streptococcus viridans*.[9, 10]

By inhibiting the body's protective mechanism of inflammation in controlling bacterial invasion, the simultaneous use of cortisone with three antibiotics may have contributed to the origin in this patient of resistant infection similar to Phillips' report of a staphylococcal septicemia and endocarditis secondary to cortisone-

treated penicillin dermatitis.[11] After discontinuance of all antibiotics in our patient with the exception of 600,000 units daily of penicillin, the decrease of pyrexia was interpreted as limitation of the spread of resistant bacterial strains.

A suddenly appearing pericardial rub in the patient on the thirty-ninth day of hospitalization, four days after discontinuance of the massive antibiotic therapy, raised again the question of concurrent rheumatic activity. Rapid increase of pulse rate as well as cardiac size with diminishing pericardial rub made the evidence of fluid collection in the pericardial space certain. Definite signs of cardiac impairment demanded pericardial aspirations on two occasions and a total of 600 cc. of dark, hemorrhagic fluid was obtained. Microscopic and cultural examinations for microorganisms in the exudate remained negative. In retrospect it seems that the most likely source of the hemorrhage into the pericardium was a ruptured mycotic aneurysm of a myocardial surface vessel. This type of aneurysm may result from bacterial invasion of the vessel wall from without or from within. Shnider and Cotsonas in their recent report [12] reviewing sixty-two cases of embolic mycotic aneurysms did not include those instances where only the proximal arch of the aorta was involved. The reason for this is the almost impossible task of deciding whether the aneurisms originate in direct extension from a diseased valve or from an embolus. Without anatomical evidence in our case, the source of the hemorrhage remains a matter of speculation.

In spite of the favorable termination of this patient's hospitalization, prognosis remains uncertain. Yet, during the several months following his discharge, he has shown further improvement and, at the time of this report, is capable of limited activity.

SUMMARY

1. A case is presented of bacterial endocarditis occurring in a previous rheumatic patient. The course was complicated by a severe hemorrhagic pericardial effusion.

2. In the absence of a specific test for active rheumatic carditis we could not exclude this disease in the beginning of the present illness.

3. The possible unfavorable effect of corticoids used simultaneously with wide-spectrum antibiotic therapy in the inflammatory stage and the spread of resistant bacteria during prolonged use of antibiotics in this patient are discussed.

4. Speculation is made about the source of the hemorrhagic effusion into the pericardium.

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An Epidemic of Influenza A-prime in a University Population

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AN EPIDEMIC of influenza A-prime occurred at Cornell University during February and March 1957. Since a high proportion of the students affected were admitted to Cornell University Infirmary, there was opportunity to study the clinical characteristics of the disease in a large group. The diagnosis was confirmed serologically in sixteen out of a representative group of twenty-one patients. The purpose of this paper is to present the results of these studies.

EPIDEMIOLOGY

The epidemic began on February 9, six days after the end of the midyear vacation, and the first case was admitted to the Infirmary on February 11.

Up to this time only localized epidemics of influenza had been reported in the U.S.A. during the winter. In December 1956 and January 1957 there had been an epidemic at the U.S. Naval Training Center, Great Lakes, Ill.,[1] and during January there had been epidemics at an Air Force base in Colorado [2] and a military installation at Memphis, Tenn.[3] A-prime virus had been isolated from all these epidemics. There had also been some scattered cases of A-prime influenza in Norfolk, Va.[4]

Concurrently with our epidemic others were reported in a boys' school in New Jersey (beginning on February 12),[5] the

University of Michigan (during the week of February 11),[6] in Washington state,[7] and among military personnel in California.[8]

METHODS

The investigation included 307 patients admitted to the Infirmary between February 11 and March 9 with an initial diagnosis of "grippe" or "upper respiratory infection."

On admission the history was recorded on a standard form, and routine physical examination was carried out by one of the two medical residents. Owing to limited laboratory facilities, it was not possible to do routine blood counts on every patient. White cell counts were performed on about 40 per cent of the patients, including all those with palpable lymph nodes, to help rule out infectious mononucleosis. Throat cultures were taken from those cases showing exudate on the tonsils or pharynx.

Chest x-rays were not taken routinely, but they were taken in all cases with abnormal physical signs in the chest, an unusually severe cough, persistent fever, or a relapse of symptoms.

Acute and convalescent phase serum specimens from twenty-one patients were sent to the Division of Laboratories and Research of the New York State Department of Health, where they were tested for antibodies against Q fever, psittacosis LGV group, adenoviruses, influenza A and B, and for cold agglutinins. These specimens were taken from patients who had been admitted during the first four days of the epidemic and were not specially selected. Throat washings in a milk medium were also collected from six cases; these were frozen and sent to the state Department of Health for isolation of virus. (We are indebted to the Division of Laboratories and Research of the New York State Department of Health for the serological studies and virus isolation and for permission to publish their results.)

RESULTS

The number of cases admitted to the Infirmary on each day of the epidemic is shown in Figure 1. Of the 307 patients admitted between February 11 and March 9, 190 were male and 117 female, out of a total student population of 7,525 males and 2,263 females. Thus 2.5 per cent of the male students and 5.1

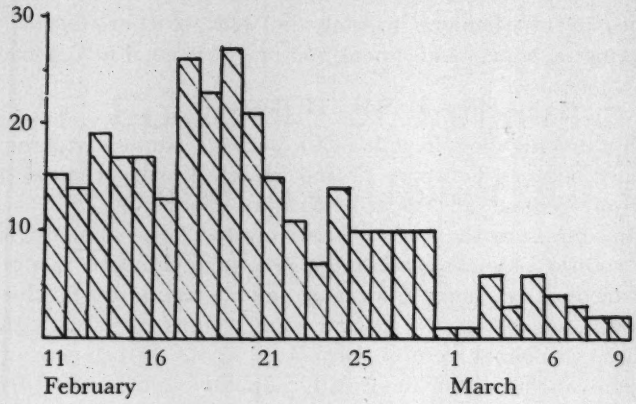

Figure 1. Daily incidence of admissions.

per cent of the female students were admitted to the Infirmary during the epidemic. The higher percentage of women is probably due to the fact that most of the female students live in dormitories where they cannot be looked after when they are sick, while many male students are known to have had the infection without coming to the Infirmary.

Clinical Features

The onset in most cases was sudden and moderately prostrating. The presenting symptoms are shown in Figure 2. The commonest symptom was a cough, which was nonproductive in most cases. Chills and fever, sore throat, headache, and nasal congestion were also noticed by the majority of patients.

The abnormal physical signs are shown in Figure 3. The most characteristic finding was a hyperplasia of the lymphoid tissue of the pharynx and fauces, which was present in over half the patients. Most of the remainder showed a generalized injection of the throat. Only eleven showed any exudate on the fauces or pharynx, and β-hemolytic streptococcus was grown on culture from six of these. Of the twenty-one patients with abnormal physical signs in the chest on admission, only two showed abnormal chest x-rays. Conjunctival injection, cervical lymph node

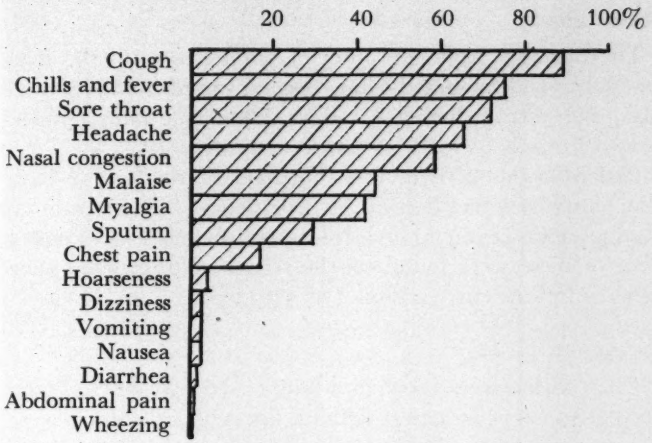

Figure 2. Presenting symptoms.

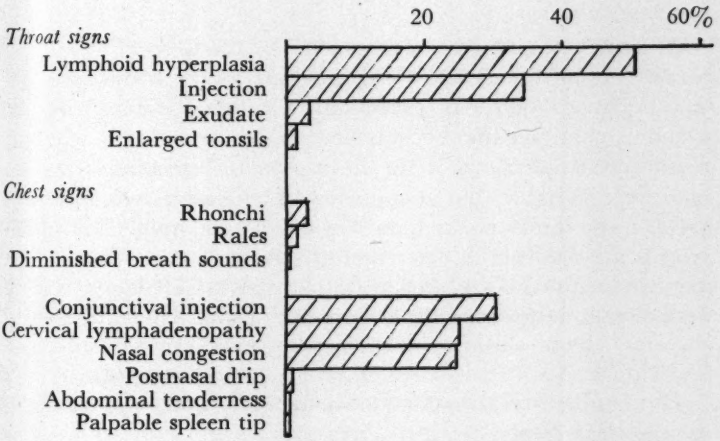

Figure 3. Physical signs.

enlargement, and nasal congestion were commonly seen. Abdominal tenderness was present in the four patients who complained of abdominal pain.

Clinical Course

The duration from the onset of symptoms until the temperature fell to and remained below normal varied from one to sixteen days, the average being 4.1 days. The maximum temperature ranged from 99.6° to 105.8°, with a mean of 102.2°.

Patients were kept in the Infirmary for at least twenty-four hours after they had become afebrile. Relapse of symptoms necessitating readmission to the Infirmary occurred in fifteen cases. Four of these were found on the second admission to have pulmonary infiltration, and one had sinusitis.

Radiological Findings

Chest x-rays were taken in a total of sixty-six cases. These were normal in fifty-two cases; definite areas of infiltration were seen in nine, an increase in the normal lung markings, in three; and abnormal density of the hila, in two.

Laboratory Findings

White cell counts were performed 144 times in 119 patients. No cases of infectious mononucleosis were found in this series. A high polymorphonuclear leucocytosis was found in four cases, of which two had pneumococcal infections (see below), and two had streptococcal infections of the throat. In the remainder the results were variable, but many showed a relative lymphocytosis between the third and sixth days of the disease, atypical lymphocytes being reported in nine cases at this stage. After the seventh day of the disease, the total count tended to be higher, with a normal ratio of polymorphs to lymphocytes.

Virus Studies

The results from the state Department of Health Laboratories are shown in Table 1.

A diagnostic rise in titre (more than fourfold) of antibodies to influenza A was shown by sixteen of the twenty-one cases, and two others showed a slight rise. The three cases that showed no rise in titre all had fairly high titres in the acute phase specimen, indicating probable previous attack.

Table 1. Results of virus studies.

Patient	*Influenza A*			*Cold Agglutinins*			*Throat Washings*	*Diagnosis*
	1	*2*	*Result*	*1*	*2*	*Result*		
C. H. S.	<4	23	Rise(x5.8)	64*	64*	No rise	Negative	Influenza A
P. M.	<4	32	Rise(x8.0)	16	16	No rise	....	Influenza A
H. D.	<4	14	Rise(x3.5)	32*	32*	No rise	....	? Influenza A
J. W.	<4	>64	Rise(x>16)	<8	<8	No rise	....	Influenza A
L. M.	16	13	No rise	<8	16	Rise(x2)	....	?
M. K.	5	13	Rise(x2.6)	32*	32*	No rise	....	? Influenza A
C. D.	<4	287	Rise(x71.8)	<8	64*	Rise(x8)	Influenza A	Influenza A
S. L.	<4	64	Rise(x16.0)	8	8	No rise	....	Influenza A
R. D.	6	32	Rise(x5.3)	8	16	Rise(x2)	....	Influenza A
J. L.	<4	24	Rise(x6.0)	16	<8	No rise	....	Influenza A
J. R.	<4	46	Rise(x11.5)	32*	16	No rise	....	Influenza A
C. B.	<4	25	Rise(x6.3)	<8	<8	No rise	....	Influenza A
B. A.	<4	55	Rise(x13.8)	<8	<8	No rise	....	Influenza A
F. S.	<4	50	Rise(x12.5)	32*	64*	Rise(x2)	....	Influenza A
C. R.	<4	19	Rise(x4.8)	<8	32*	Rise(x4)	....	Influenza A
B. N.	28	50	No rise	64*	64*	No rise	....	?
M. Z.	<4	>64	Rise(x>16)	16	16	No rise	Influenza A	Influenza A
J. M.	<4	28	Rise(x7.0)	<8	<8	No rise	Negative	Influenza A
R. H.	14	23	No rise	16	32*	Rise(x2)	....	?
V. R.	<4	25	Rise(x6.3)	<8	<8	No rise	....	Influenza A
L. H.	<4	32	Rise(x8.0)	32*	16	No rise	Influenza A	Influenza A
R. Z.	...	...	....	...	...	....	Negative	?

* Abnormally high titres.

No significant rise of antibodies to the adenoviruses, influenza B, Q fever, or the psittacosis LGV group was shown in any case, although one case (B. N.) showed very high titres to adenovirus. A definite rise in cold agglutinins (more than fourfold) was seen in two cases, and seven others showed abnormally high titres (1: 32 or greater). None of these patients showed any clinical evidence of viral pneumonia, and chest x-rays taken in three of them were normal. Influenza A-prime virus was isolated from the throat washings in three of the six cases, the other three being negative. These results have been reported in the Morbidity and Mortality Weekly Reports of the U.S. Department of Health, Education and Welfare, for March 22, April 5, and April 19, 1957.

Pulmonary Complications

Such complications occurred in twelve patients in the series. Two of these were pneumococcal infections, characterized by high temperatures (maximum 104.8° and 104.4° respectively), polymorphonuclear leucocytosis (76 per cent of 34,000 and 8? per cent of 30,000), radiological signs (increased density of the hilum in one and infiltration of the right costophrenic angle in the other), and recovery of pneumococcus from the sputum. These patients responded rapidly to antibiotic therapy with tetracycline, their temperatures falling to normal within twenty-four hours of starting treatment.

The other ten pulmonary complications were thought to be due to viral infection. Four of the patients had been discharged from the Infirmary after becoming afebrile but had relapsed between the sixth and ninth days from the onset, and chest x-ray on the second admission revealed an area of pulmonary infiltration. One patient had run a prolonged febrile course, with a negative chest x-ray on the ninth day of the disease, but pulmonary infiltration was found on the fourteenth day. The other five patients were found to have pulmonary infiltration or increased lung markings at the time of admission. White cell counts in these patients did not differ significantly from those of patients without pulmonary infiltration. Their fever persisted for from three to sixteen days and was not influenced dramatically by tetracycline therapy.

Cold agglutinins were determined in six of these patients. Two showed a fourfold rise in titre between the acute and convalescent phase, and one showed a titre of greater than 1: 512 even in the acute phase. The other three showed no rise.

DISCUSSION

The A-prime strain of influenza first appeared in the United States in the winter and spring of 1947, and this strain has been responsible for most of the epidemics since then.

Kilbourne and Loge [9] reported one of the first epidemics (at Fort Monmouth, N. J.) and analyzed the symptoms and signs in seventy-six patients from the peak of the epidemic. The clinical

picture in our epidemic did not differ greatly from that described by these men. The marked hyperplasia of lymphoid tissue in the throat, which was the most characteristic physical sign in our patients, may have been due to the age group we were studying, almost all of whom were between seventeen and twenty-four years old.

The proportion of patients showing pulmonary infiltration varies greatly from one epidemic to another. Nine of our 307 patients (2.9 per cent) showed infiltration at some stage. In Kilbourne and Loge's series, only one of their seventy-six cases showed infiltration. However, in an epidemic at the U.S. Naval Hospital, Philadelphia, in 1951, Scher and Jaruszewski [10] reported pulmonary infiltration occurring in twenty-four of their seventy-six cases (31.6 per cent). This infiltration was thought to be due to the influenza virus itself.

There were no serious complications in our series, the two patients with secondary pneumococcal infections responding very rapidly to antibiotic therapy.

The diagnosis was confirmed serologically in 76 per cent of the cases tested. In the Fort Monmouth and Philadelphia epidemics there was serological confirmation in about 80 per cent. The high titres of cold agglutinins in 33 per cent of the cases with serologically proven influenza and without pulmonary infiltration was an unexpected finding. Scher and Jaruszewski found positive cold agglutinin titres in three of their seventy-six cases, two of which had pulmonary infiltration. Previous reports on cold hemagglutination [11, 12] have indicated that this occurs almost exclusively in "primary atypical pneumonia," and they have not demonstrated its occurrence in influenza. Hemagglutination reactions with suspensions of influenza virus were studied experimentally by Overman and Friedewald,[13] who found that these suspensions would agglutinate sheep and rabbit red cells in high titre at 4° C but not at room temperature. Human red cells which had first been treated with virus and then stabilized with formalin could then be agglutinated by the same procedure. However, there have been no reports of cold agglutination reactions occurring with the serum of patients suffering from influenza.

SUMMARY

An epidemic of influenza A-prime in 307 university students is reported, and the clinical features and course of the disease are described.

The diagnosis was confirmed serologically in sixteen of the twenty-one cases tested, and virus was isolated from three cases.

Two patients developed a secondary pneumococcal infection, and ten others showed evidence of viral pneumonia.

Cold agglutination titres were found to be abnormally high in seven of the sixteen serologically proven cases, none of which showed any evidence of pulmonary infiltration.

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Case Reports of the Cornell University Infirmary and Clinic

Dr. Haringa: "This is the case of an eighteen-year-old girl who was admitted to the Infirmary last fall complaining of sore throat, hoarseness, and cough of about six days' duration. Her family history was not remarkable. She gave a past history of the usual childhood contagious illnesses without any complications. She had had sinusitis twice during childhood and had had rather mild hay fever. She gave a history of being jaundiced at birth and told us she was transfused at the time. Subsequent information indicates that this was diagnosed as physiological jaundice and so may not be relevant to the present illness. She had had moderate facial acne for about a year and had received treatment from a dermatologist. A routine physical examination in January 1956 revealed essentially normal findings except for the acne and a basal metabolic rate of minus thirteen. Because of these she was given one-half grain of thyroid per day. She took this regularly until her admission. Menarche had occurred at age sixteen, and her menses had been regular for a time but then stopped, so that she had had amenorrhea for the past ten months. She didn't take this seriously, however, because her mother told her that she had had such a period of amenorrhea for several months during her youth with spontaneous recovery.

"Her present symptoms of respiratory tract infection had begun six days prior to admission. Three days before admission she was seen at the cold clinic. Her temperature was 97.8° and she was given symptomatic treatment. She continued to have symptoms, however, and returned to the cold clinic. Because of the additional complaint of pain in the right ear she was referred to

me. Her ears were normal, the pharynx was injected, the tonsillar nodes were palpable and slightly tender, and she had a temperature of 97.4°. There were some crepitant rales in the right base, and she was sent to the infirmary with the presumptive diagnosis of viral pneumonia. She had had no chest pains, chills, sweats, or fever. At the Infirmary the previous findings were confirmed. She had a rectal temperature of 100.4°. A chest x-ray on the following day showed generalized increase in the pulmonic markings of the lower two-thirds of the right lung field and in the perihilar area on the left. A white blood cell count at this time was 6,400 with 62 per cent neutrophils, 25 per cent lymphocytes, 5 per cent monocytes and 8 per cent eosinophiles, and there was a note to the effect that the smear showed red cells which were achromic and showed marked anisocytosis. She was started on tetracycline, 250 mg. four times a day, which was continued for five days. Her respiratory symptoms gradually cleared during that time, and four days after the original chest film another x-ray showed lung markings to be essentially normal. Her temperature fell gradually from 101° to normal six days later.

"A cue was taken from the report on the smear, a red blood cell count and hemoglobin determination were ordered, and these were reported as 3,250,000 red cells and 8.2 gm. of hemoglobin. When questioned, she said she had noticed some shortness of breath and easy fatigability on climbing hills for about three weeks but hadn't given this much thought. She also recalled a remark by her roommate to the effect that she appeared pale. Two days after admission it was noticed that she was jaundiced. Examination at that time showed both the liver and spleen to be palpable about two fingerbreadths below the costal margin, the liver being slightly tender. The total bilirubin two days after admission was 4.25 mg.—direct 3 mg., indirect 1.25 mg. Her thymol turbidity was 14.2 units and cephalin flocculation 4 plus. The total protein was 9.4 gm. with 4.3 gm. of albumin and 5.2 gm. of globulin. She had no symptoms suggestive of hepatitis. Her appetite was good, and she said she felt very well; in fact she continually asked to be allowed to go out and take her scheduled examinations. She was kept on bed rest, however, and was given the usual treatment of high protein, high calorie diet with sup-

plementary vitamins. Ferrous gluconate was given for the anemia. Additional laboratory investigation yielded the following results: L.E. cell preparation, negative; heterophile antibody test, negative; reticulocyte count 0.2 per cent; sedimentation rate 60 mm. per hour (Wintrobe); cholesterol 82 mgm. per cent). A red blood cell fragility test showed greater resistance than the control.

"About two weeks after admission, her liver was felt with difficulty but descended one fingerbreadth below the costal margin, and the spleen was barely palpable. She was still jaundiced. Her total bilirubin when she left here was 3.5 mg., and the anemia had improved slightly, the hemoglobin having increased to 9.5 gm. She was discharged on the sixteenth hospital day and taken home by her parents for further convalescence. Liver function tests were repeated there and were persistently abnormal. She was admitted to another hospital where she remained for thirty-six days. She continued to feel well all this time. On admission to that hospital, she had moderate scleral icterus and a yellowish cast to her skin. Some pin-point red spots which blanched with pressure were noted on the arms and trunk, but apparently these didn't look like true spider angiomata. A few typical angiomata were noted later by her physician, and these disappeared after steroid therapy was instituted. The liver was felt 6 cm. below the costal margin; her spleen was not felt at this time. The routine urinalysis showed normal results, except for the presence of a slight amount of bile. Her hemoglobin at this time was 11.8 gm., the white count was 5,000 with 39 per cent neutrophiles, 20 per cent band forms, 28 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophiles and 8 per cent basophiles. Subsequent blood counts were essentially normal. Feces was guiac negative. The BMR was minus 16 and protein-bound iodine was 3.9 micrograms. An L.E. cell preparation was negative, as it had been here. A bone marrow examination showed slight erythroid hyperplasia. Further results included a positive Coombs test, alkaline phosphatase 4.3 units, total bilirubin 3.8 mg., thymol turbidity 19 units, cephalin flocculation 22, bromsulfalein 48 per cent retention, and cholesterol 137 mg. with 63 per cent esters. The prothrombin time was 16.3 sec. as compared with a control of 14.5 sec. The total protein had continued to rise, going up to

11.2 gm. with 2.3 gm. of albumen and 8.9 gm. of globulin. Some transaminase determinations on admission showed 1,326 units as compared to the normal upper limit of about 40 units. This went up further, reaching a maximum of 2,650 units; finally on prednisone therapy it came down to 220 units. An esophagram was done and showed no varices; a chest x-ray was normal. She was started on prednisone in a dosage of 60 mg. per day for the first twelve days. Her transaminase level fell precipitously; the bilirubin came down, and the total proteins fell to 7.7 gm.; the albumin being 2.3 and the globulin 5.4 gm.

"After her discharge further tests showed a cholesterol value of 397 and a hemoglobin of 14.2 gm. The discharge diagnosis was Eisenmenger's cirrhosis. Dr. Evans will carry on the discussion from here."

Dr. R. Evans: "This case seems to be an example of a syndrome which has only relatively recently been recognized. For information about it I read an article by Bearn and others [1] in the July 1956 number of the *American Journal of Medicine* in which the authors report twenty-six cases of cirrhosis of unknown etiology occurring in patients under thirty-four. This group of patients was found to exhibit certain characteristics which were not normally seen in either Laennec's cirrhosis or posthepatitis cirrhosis. Of the twenty-six patients, twenty-three were females, and their ages at onset ranged from three to thirty-three years, twenty of them beginning between the ages of ten and twenty years. All of these patients had developed cirrhosis insidiously without any definite preceding attack of infectious hepatitis. Seven of the twenty-six had possibly had an atypical attack of hepatitis, but they showed changes similar to the other nineteen, who had no such history, and their symptoms were unlike the usual picture of posthepatitis cirrhosis.

"The clinical characteristics of this group were, first of all, amenorrhea or delay in menstruation: this was seen in fifteen of the twenty-three women patients at the onset and developed during the course in five others, so twenty of them altogether showed it at some stage. Three of them gave a history of having taken

[1] A. G. Bearn, H. G. Kunkel, and R. J. Slater, The Problem of Chronic Liver Disease in Young Women, *Am. J. Med. 21:* 3–15, 1956.

estrogens to try to stimulate menstruation. Weight increase during the preceding year was noted in some of the patients, and two of them had been given thyroid on this account. The onset in all cases was insidious, often beginning with a symptomless jaundice, or sometimes with exertional fatigue, lassitude, or bleeding from the gums. Acne was commonly seen in these patients, and some of them exhibited hirsutism, pigmented striae and moon-faces. Another symptom seen in ten of these cases was obscure episodes of fever, sometimes accompanied by respiratory or cardiac symptoms. During such an episode in one patient L.E. cells were found in the blood, but this could not be demonstrated in any of the others. Joint pains occurred from time to time in eleven patients, sometimes accompanying the febrile episodes, and three patients developed chronic joint changes resembling rheumatoid arthritis, while two others showed rheumatic nodules. The classical signs of cirrhosis gradually developed in all of these cases, although most of them were well nourished and appeared healthy. Enlargement of the liver and spleen was commonly found and later spider angiomata and liver palms were seen in the majority. Esophageal varices developed in twelve of them and bleeding from these occurred in eleven. Ascites was uncommon in this group but occurred in some in the final stages.

"Most characteristic of the laboratory findings was a hypergammaglobulinemia in the early stage of this syndrome. The average total protein in the group reported was 9.3 gm., and in ten patients total proteins of over 10 gm. were found. It was found gradually to diminish as the disease progressed, the albumin decreasing as well as the globulin and eventually approaching the usual findings for Laennec's cirrhosis. The serum bilirubin was found to fluctuate, usually ranging between 3 and 5 mgm. per cent.

"If we look at these characteristics and compare them with the findings in the case which has been presented, we see that our patient had had amenorrhea for about ten months. The onset was certainly insidious (the respiratory infection probably being incidental), and she developed liver and spleen enlargement, jaundice, and anemia with very few symptoms. She had had acne for about a year before she came in. She did not manifest any

febrile episodes, except the respiratory infection, and she did not have any joint pains. She was thought at New York Hospital to have some spider angiomata. She certainly had hypergammaglobulinemia, and her serum bilirubin was moderately raised.

"Liver biopsies were done in several of the cases reported in this series, but this has not been done in our case. The pathology shows a diffuse nodular cirrhosis resembling the postnecrotic type, with large nodules of variable size. In the acute stages of the disease, when the gamma globulin level was very high, infiltration with inflammatory cells was seen characteristically in the liver, with small areas of necrosis and strands of fibrous tissue. The commonest inflammatory cells were found to be plasmacytes, together with fibroblasts, lymphocytes, and macrophages. A positive correlation was found between the presence of plasmacytes and a high gamma globulin. In the chronic stage of the disease fibrocytic proliferation was found.

"There are three theories of the etiology of this condition, put forward by Bearn and his co-workers. The first is that it may in fact be a posthepatitis cirrhosis, assuming the patient to have had a cryptic form of infectious hepatitis, without any symptoms, which had gone on to a cirrhosis. However, such a marked incidence in women has not been noted in posthepatitis cirrhosis. Arthralgia is uncommon, although it has been described in some cases following hepatitis, and hypergammaglobulinemia is also uncommon, although it may sometimes occur in the early stages of posthepatitis cirrhosis. The second possibility is that some endocrine influence in this particular age group (most of them have begun within a few years of puberty) may possibly modify the effects of the infectious hepatitis virus and cause an unusual form of the disease. The third possible theory is that it is some form of collagen disease. This is suggested by the generalized effects, febrile episodes, joint changes, and in some patients involvement of the pericardium and lungs and is possibly supported by the fact that L.E. cells were found in one case in this group, although these cells have been described in two cases of active chronic viral hepatitis. Cirrhosis does not usually occur in lupus erythematosus, and most of the typical features of that disease are absent in this group.

"What of the prognosis of this condition? In this series of patients twelve out of the twenty-six have died, the average duration from the time of onset to death being seven years. Of those still alive the mean duration is five and a half years, and the longest any has survived and remained relatively well is twelve years. On the whole it seems that the average expectation of life after this disease has begun is less than ten years.

"The patients in this series were all treated with a nutritious high protein diet, salt being restricted if necessary. Bed rest was only advised during the febrile episodes, otherwise graded forms of activity were permitted. In five of the patients estrogens were given to see if they had any effect, and they were found to increase the depth of jaundice in all five. The use of ACTH and cortisone in the treatment of liver disease was reviewed by Sborov and his associates [2] in May 1955. They concluded that the results were very unpredictable and that these drugs should not be given routinely, but only if there were specific indications. In acute hepatitis they recommended that these drugs should only be given when the jaundice is unusually deep or sustained for several weeks and in certain cases that relapse after the initial treatment. In chronic hepatitis, in which symptoms and laboratory findings of liver disease persisted for more than six months after an acute attack, eight of eighteen patients showed improvement on cortisone or ACTH, but the remainder did not show any improvement. In cirrhosis of the liver four out of the nine cases in their report showed improvement in general well being and of their liver function, but in these cases there is some danger of provoking bleeding from esophageal varices and of promoting salt and water retention. In Bearn's series of twenty-six young patients in this group with cirrhosis, cortisone was tried in some and was found to increase the general well being with diminution of the size of the liver and the spleen and improvement in the serum proteins and the bilirubin. However, there was no definite evidence that it modified the course of the eventual outcome of the disease, although withdrawal of cortisone was followed by a

[2] V. M. Sborov, L. W. Bluemle, Jr., J. R. Neefe, and P. Gyorgy, The Clinical Usefulness of ACTH and Cortisone in Liver Disease, *Gastroenterology 28:* 745–758, 1955.

relapse of symptoms in two patients, who again improved when it was resumed.

"I thought I would also comment on the use of the serum transaminase levels in the investigation of hepatic disease. Glutamic oxaloacetic transaminase was first described in 1955 by LaDue and Wroblewski,[3] who discovered that this enzyme is normally present in heart muscle, skeletal muscle, brain, liver, and kidney in increasing amounts. The normal activity of this enzyme in the serum (SGO-T) ranges from 5 to 40 units. They discovered that this was increased in cases of acute damage to the heart muscle, skeletal muscle, or liver and was useful in the diagnosis of myocardial infarction where the SGO-T value rises 2 to 20 times. It was soon found that in active liver disease it was raised to a greater extent, and often 2 to 100 times normal. This was postulated to be due to the release of the intracellular enzyme from the damaged cells, and the value was thought to be proportional to the amount of cell damage present. The same workers investigated the SGO-T in various types of liver disease.[4] In epidemic infectious hepatitis they found that in 19 out of 20 patients the SGO-T was more than 300 units and in 4 of them it was over 1,000 units. The majority returned to normal in four weeks and all of them had returned to normal by eight weeks: if a relapse occurred, this was accompanied and some times preceded by a rise in the SGO-T. They investigated twelve patients with homologous serum hepatitis and 9 of these had raised SGO-T to more than 750 units; the other patients were all seen in the later stages of the illness and had rises of a lesser degree. In infectious mononucleosis three cases complicated by hepatitis showed a rise in the transaminase, but the uncomplicated cases showed no rise. In cirrhosis the SGO-T is normal in fully compensated cases, but when the disease is active it is elevated to a lesser degree than in hepatitis, about 40 to 300 units. If acute hepatitis intervenes on top of cirrhosis, the value rises to high

[3] J. S. LaDue and F. Wroblewski, The Significance of the Serum Glutamic Oxaloacetic Transaminase Activity following Acute Myocardial Infarction, *Circulation 11:* 871–877, 1955.

[4] F. Wroblewski, G. Jervis, and J. S. LaDue, The Diagnostic, Prognostic and Epidemiological Significance of Serum Glutamic Oxaloacetic Transaminase Alterations in Acute Hepatitis, *Ann. Int. Med. 45:* 801–811, 1956.

levels. In primary or secondary carcinoma involving the liver seventy-five out of one hundred cases showed an elevation of from 45 to 250 units, and in extrahepatic bilary obstruction the SGO-T was shown to rise to 100–300 units, but it fell rapidly again when the obstruction was relieved. So it was concluded that this SGO-T gave a roughly proportional indication of hepato-cellular damage. Complications, relapses, or chronicity superimposed on an acute hepatitis are reflected in variations from the usual pattern of serial SGO-T changes seen in hepatitis. It is thought probable that the initial rise takes place from one to four weeks before the onset of jaundice, so it may enable nonicteric cases to be diagnosed.

"A still more recent report from the same writers,[5] in November 1956, gives preliminary information on yet another enzyme of this transaminase group—serum glutamic pyruvic transaminase (or SGP-T). The concentration of this enzyme is relatively greater in the liver than it is in any other tissue; the heart and skeletal muscles contain a lesser amount, so it is not found to be raised in most cases of myocardial infarction, although in extensive infarctions where there is a very high level of the SGO-T, there may be expected to be a smaller rise of the SGP-T. In epidemic infectious hepatitis and in serum hepatitis the SGP-T was found to be greatly raised and in each case was found to be of a higher level than the SGO-T. In extrahepatitic biliary obstruction also, the SGP-T was found to be higher than the SGO-T. However, in chronic liver disease such as cirrhosis or metastatic carcinoma, the SGP-T was found to be raised less often than the SGO-T and to a lesser degree. So we have two enzymes here which reflect liver damage. The SGP-T seems to be the more sensitive in acute hepato-cellular damage, while the SGO-T is the more sensitive in chronic hepatic disease. What causes this difference between them is not yet known.

"In our patient presumably the type of transaminase determined was the SGO-T. The results were very high, going up as far as 2,650 units, but with the administration of prednisone it fell rapidly toward a normal level, so it looks as if the active cellular damage in the liver is coming under control."

[5] F. Wroblewski and J. S. LaDue, Serum Glumatic Pyruvic Transaminase in Hepatic Disease: A Preliminary Report, *Ann. Int. Med. 45:* 801–811, 1956.

Dr. Wightman: "What is the name of this condition?"

Dr. Evans: "The diagnosis made was 'Eisenmenger's cirrhosis' —I haven't found any reference to this name in any literature so far. The description in the article I have been commenting on was of 'chronic hepatic disease in young women.' "

Dr. Wightman: "Is she taking oral cortisone now?"

Dr. Evans: "Yes. As far as we know 15 mg. of prednisone per day."

Question: "What reference was made to anemia in the other cases?"

Dr. Evans: "No reference at all was made in Bearn's series to anemia. I assume the anemia was related directly to her liver disease; it certainly has improved as she has gone along; her hemoglobin is now 14.2 gm."

Question: "What role did preceding virus pneumonia play? I do not think it can be called a coincidence that she had a fairly severe lung infection before getting her first attack of jaundice."

Dr. Evans: "I think probably the infection superimposed on the liver damage brought it to light, but I think the results show, particularly the serum proteins, that the liver damage must have antedated the acute infection of the lung."

Question: "Is it possible that this might be an end result of nonicteric infectious hepatitis?"

Dr. Evans: "Yes, as was pointed out, this picture is somewhat different from that usually seen in posthepatitis cirrhosis, in which it is not usual to find joint pains, febrile episodes, and amenorrhea."

Dr. Moore: "I talked with Dr. David Barr about this. He immediately spotted two symptoms, the amenorrhea and the acne as most suspicious and most characteristic of this disease together with the laboratory findings. I think that hypergammaglobulinemia, amenorrhea, and acne are almost pathognomonic of this disease."